THE THERAPEUTIC VALUE OF VITAMINS A & D IN MEASLES

BY

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Objects of investigation.

The investigation described in this communication was planned with two main objects in view; first, to determine whether the administration of vitamin D, or of vitamins D and A, to children with measles had any favourable influence on the course of the disease; and secondly, to determine whether vitamin A would lessen the incidence of the minor skin infections common in measles. J. B. Ellison's work[1] on measles at the Grove Hospital in London suggested that the combined administration of vitamins D and A lessened the mortality, but there was the apparently discrepant finding that the incidence of otorrhoea in his cases was not favourably affected. So far as the present authors are aware, no series of cases has yet been published in which the therapeutic value of these vitamins has been satisfactorily established for an already existant acute infection. On the other hand, there is much to indicate that resistance to infections is reduced in children suffering from an overt deficiency of either of these vitamins[2]. Hence it seemed that Ellison's tentative findings, as he himself said, required corroboration. A previous investigation undertaken by Mackay[3] suggested that the earliest evidence of vitamin A deficiency in infants might be an increased susceptibility to skin infections, and a study of the literature reveals that such infections are common with overt vitamin A deficiency[4]. In measles, infections of the skin and mucuous membranes are common. It was, therefore, hoped that if some of the children suffered from a deficiency of vitamin A, the addition of this substance to their diet would diminish the number of such infections, and provide corroborative evidence of the findings with infants.

Clinical material and scheme of investigation.

The present investigation was carried out at the North Eastern Hospital, London, between January and July, 1934. The children admitted were for the most part from families sending their children to London County Council schools, that is they belonged to lower middle class and labouring

class families. The children were of a similar social type to those dealt with by Ellison.

The total number of cases was 713; of these sixteen were subsequently excluded because they were under observation for less than seven days, having been transferred to other wards with another infection, such as whooping cough, diphtheria, chicken pox and enteritis, leaving 697 included in the investigation. The ages varied from two months up to twelve years: 365 were boys and 332 girls.

The children were divided into three groups. All were given the routine diet customary in the hospital. The first group served as controls and received no extra vitamin medication; the second group were given a vitamin D supplement, the third a supplement of vitamin D and vitamin A combined.

The children were under the care of three medical officers. During the first few weeks of the observation M. M., and for the remainder of the time H. L. and M. W. had charge of the children and kept the clinical records on an agreed scheme, an effort being made to co-ordinate findings. When, for example, there was uncertainty as to a diagnosis, M. M. and H. M. M. M. usually also examined the cases, with the object of arriving at findings which were generally agreed. Five wards were allocated to the children under investigation; three wards being under the charge of H. L. and two under that of M. W. Cases admitted into each ward were included in rotation in each of the three groups. By this means it was hoped to ensure that in each ward and under each medical officer there should be equal numbers of each of the groups, so that the results might not be complicated by differences in ward technique. During the course of the observation, when the number of children had reached about 300, it was found that the groups were not evenly balanced as regards age and presence of pneumonia on admission. In order to rectify this a notice was thenceforward put up in the admission room at the beginning of each week requesting, for example, that the next two children aged one year admitted with pneumonia should be placed in group X, or the next four children aged two years should go into group Y, etc. Apart from this modification the scheme of allocation to the three groups in rotation was continued.

The tabulation of records was carried out by H. M. M. M., with the help of Miss Lorel Goodfellow. Since one person tabulated the findings in all cases this should ensure uniformity of standard in this section of the work.

Diet in hospital and vitamin supplements.

The children during the pyrexial stage of the illness were fed chiefly on milk or milk and cereal. When convalescent the older children received fish or meat and green vegetables at dinner, with a total of one pint of milk and one ounce of butter daily. Unless specially ordered no eggs were given to any children under seven years old and no raw fruit was officially included in the dietary although some fruit was sent in by the parents. The vitamin supplements were prepared and standardized by the British Drug Houses Ltd. The vitamin D group received 3,000

international units in the form of calciferol daily. This is the nominal equivalent in international vitamin D units of, say, one ounce of cod-liver oil daily; or, what is perhaps more relevant, it is enough to produce in a child healing of active rickets at what would appear to be the maximum rates[5]. The D plus A group received the same amount of vitamin D, and, in addition, the vitamin A equivalent of six drachms of cod-liver oil of 7·5 blue value daily. The vitamins were incorporated in an emulsion made with carrageen and acacia.

Results.

Total fatality rate.—The total number of fatal cases is small (33 deaths among 697 cases; a fatality rate of 4·7 per cent.), and this must be borne in mind in relation to the fact that the case mortality in the three groups is fairly close. Among controls it is 4·3 per cent.; among D cases 4·1 per cent.; and among D plus A cases 5·9 per cent. (see table 1). Thus

TABLE 1.

DEATHS: ALL CAUSES.

	CONTROLS.			D CASES.			D + A CASES.			ALL GROUPS COMBINED			
	No. OF CASES	DEATHS	CAUSE OF DEATH	No. OF CASES	DEATHS	CAUSE OF DEATH	No. OF CASES	DEATHS	CAUSE OF DEATH	No. OF CASES	DEATHS	DEATHS PER 100 CASES	
UNDER 1 YEAR	26	1	P. 1	26	5	P. 3, Ent. 2	25	2	P. 2	77	8	10.4	9·9
1 YEAR OLD ...	69	6	P. 5, Enc. 1	69	4	P. 3, S. 1	67	10	P. 10	205	20	9·8	
2 YEARS ...	63	1	P. 1	62	1	P. 1	61	0	—	186	2	1·1	1·4
3 ,, ...	33	1	P. 1	33	0	—	28	1	P. 1	94	2	2·1	
4 ,, ...	22	0	—	25	0	—	17	0	—	64	0	—	0·7
5 ,, ...	11	1	P. 1	15	0	—	13	0	—	39	1	2·6	
6 YEARS AND OVER	10	0	—	11	0	—	11	0	—	32	0	—	
TOTAL	234	10	P. 9, Enc. 1	241	10	P.7 Ent.1, S.1	222	13	P. 13	697	3	4·7	
FATALITY PER 100 CASES ...		4·3			4.1			5·9			4·7		
DEATHS OCCURRING AFTER 7 DAYS IN HOSPITAL: NO. ...		6			6			7			19		
FATALITY PER 100 CASES ...		2·6			2·5			3·2			2·7		

P. = pneumonia; Enc. = encephalitis; Ent. = enteritis; S. = septicaemia.

the first two groups have all but the same fatality rate, and the D plus A cases a slightly higher rate. If all children dying within one week of admission are omitted, i.e., if only those are considered who had seven days treatment and upwards the comparative results are similar: the fatality rates being 2·6 per cent., 2·5 per cent. and 3·2 per cent. respectively. Again there is no evidence of any favourable effect on the fatality rate from the vitamin administration.

Analysis of fatality rates in the three groups.—It is obviously necessary to examine whether the groups were evenly matched on admission before judgment can be passed on the deductions drawn. It is well known that the fatality rate from measles varies widely with age: if the three groups are combined it is found that of those under two years old 9·9 per cent. died, of those two and three years old 1·4 per cent. died, and of those of four years and over only 0·7 per cent. died (see table 1). Table 1 and table 2, however, show that the number of children in each age division was similar in the three groups, hence the results are not vitiated by discrepancies in age between the three groups.

TABLE 2.

AGE: DISTRIBUTION OF CASES.

	CONTROLS		D CASES		D + A CASES		ALL GROUPS COMBINED	
	No.	PER CENT.	No.	PER CENT.	No.	PER CENT.	No.	PER CENT.
UNDER 2 YR.	95	41	95	39	92	41	282	40
2 & 3 YR. OLD	96	41	95	39	89	40	280	40
4 YR. & UPWARDS	43	18	51	21	41	18	135	19
	234		241		222		697	

Another obvious factor influencing the fatality rate is the incidence of pneumonia at the time of admission. Of the total number of deaths (i.e., 33) 29 (or 88 per cent.), were due to pneumonia, and of these 29 children 25 had pneumonia on admission (which accounts for 76 per cent. of the total 33 deaths), and four developed pneumonia after admission. Of the remaining four deaths, two were due to enteritis, one to septicaemia and one to encephalitis, these complications developing after admission. As already stated, the attempt was made to allocate equal numbers of children with pneumonia on admission to each group. The distribution of cases is shown in tables 3 and 4. Considering each group as a whole, the incidence of pneumonia on admission is similar:—controls 13·2 per cent.; D cases 12·0 per cent.; D plus A cases 12·6 per cent.; and the distribution of pneumonia among children of different ages is fairly even between the three groups. This is more easily seen in table 4, where it is shown that among children aged less than two years, and in those aged two years and three years, the incidence of pneumonia on admission is almost identical in the three groups; and of the 33 deaths, 32 were in these age periods.

TABLE 3.

FATALITY AND PNEUMONIA INCIDENCE ANALYSED.

	CONTROLS					D CASES					D + A CASES					ALL GROUPS COMBINED				
	PNEUMONIA ON ADMISSION		PNEUMONIA AFTER ADMISSION		TOTAL DEATHS ALL CAUSES	PNEUMONIA ON ADMISSION		PNEUMONIA AFTER ADMISSION		TOTAL DEATHS ALL CAUSES	PNEUMONIA ON ADMISSION		PNEUMONIA AFTER ADMISSION		TOTAL DEATHS ALL CAUSES	PNEUMONIA ON ADMISSION		PNEUMONIA AFTER ADMISSION		TOTAL DEATHS ALL CAUSES
	No.	Died	No.	Died		No.	Died	No.	Died		No.	Died	No.	Died		No.	Died	No.	Died	
UNDER 1 YEAR ...	2	1	1	—	1	5	3	2	—	5	3	1	1	1	2	10	5	4	1	8
1 YEAR OLD	15	5	7	—	6	11	3	1	—	4	14	7	9	3	10	40	15	17	3	20
2 ,, ...	7	1	1	—	1	9	1	1	—	1	7	—	2	—	—	23	2	4	—	2
3 ,, ...	3	1	2	—	1	1	—	—	—	—	4	1	—	—	1	8	2	2	—	2
4 ,, ...	2	—	—	—	—	1	—	—	—	—	—	—	—	—	—	3	—	—	—	—
5 ,, ...	1	1	1	—	1	1	—	—	—	—	—	—	—	—	—	2	1	1	—	1
6 YEARS AND OVER ...	1	—	1	—	—	1	—	—	—	—	—	—	—	—	—	2	—	1	—	—
TOTALS	31	9	13	—	10	29	7	4	—	10	28	9	12	4	13	88	25	29	4	33
PER CENT. OF TOTAL CASES	13·2	3·8	5·6	—	4·3	12·0	2·9	1·7	—	4·1	12·6	4·1	5·4	1·8	5·9	12·6	3·6	4·2	0·6	4·7

	CONTROLS			D CASES			D + A CASES			ALL GROUPS COMBINED		
TOTAL NO. OF CASES OF PNEUMONIA.	No. 44	No. died 9	per cent. died 20·5	No. 33	No. died 7	per cent. died 21·2	No. 40	No. died 13	per cent. died 32·5	No. 117	No. died 29	per cent. died 24·8

TABLE 4.

AGE—DISTRIBUTION OF CASES OF PNEUMONIA ON ADMISSION.

	Controls			D cases			D + A cases		
	No. of cases	Pneumonias No.	Pneumonias Per cent.	No. of cases	Pneumonias No.	Pneumonias Per cent.	No. of cases	Pneumonias No.	Pneumonias Per cent.
Under 2 yr.	95	17	18	95	16	17	92	17	18
2 & 3 yr. old	96	10	10	95	10	11	89	11	12
4 yr. & upwards	43	4	9	51	3	6	41	0	0
		31			29			28	

In these cases the fatality rate varied appreciably according to the season of the year during which they were admitted. Thus there were 27 deaths among 426 cases admitted in January to April, a fatality of 6·3 per cent.; whereas among 271 cases admitted in May to July there were only six deaths, a fatality of 2·2 per cent. Table 5 shows that though the percentage of each group admitted in the months January to April did not differ widely, a slightly larger proportion of D plus A cases was admitted in these more unfavourable months. However, the fatality figures in table 5 show that if cases admitted during either January to April, or May to July, are separately compared, there is still no evidence of advantage from vitamin administration.

TABLE 5.

SEASON OF ADMISSION: DISTRIBUTION OF CASES AND FATALITY.

	January—April				May—July			
	Cases		Deaths		Cases		Deaths	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Controls	137	58·5	7	5·1	97	41·5	3	3·1
D cases	147	61·0	10	6·8	94	39·0	0	0·0
D + A cases	142	64·0	10	7·0	80	36·0	3	3·8

TABLE 6.

FATALITY RATES IN RELATION TO THE STAGE OF THE ILLNESS ON ADMISSION.

Stage of disease on admission:	1st day of rash	2nd day of rash	3rd day & later	Before rash	Developed measles in hospital
A. All cases.					
No. of cases	350	203	114	28	2
No. died	10	8	13	2	—
Per cent. died	2·9	3·9	11·4	7·1	—
			10·6		
B. Cases under 2 yr. old.					
No. of cases	6·5	79	51	11	2
No. died	9	8	9	2	—
Per cent. died	139	10·1	17·6	18·2	—
			17·7		

A relation also exists between the stage of the disease at which children were admitted and the fatality rate. The fatality rates according to the stage of the disease on admission are shown in table 6. The lowest fatality is shown by the cases admitted on the day the rash came out; it is higher for those admitted on the second day of the rash; and highest for children admitted either earlier or later than these dates. Probably these figures indicate that cases coming in before the rash developed, or after the rash had been out for two days, tended to be children who were sent in because they were seriously ill. If the distribution of cases among the three groups is examined according to the stage of the disease on admission, it is found that the D plus A group was at a distinct disadvantage because a considerably larger proportion of the young children in this group were admitted either before the appearance of the rash or on or after the third day of the rash (table 7). Hence it is probable that the D plus A group contained a

TABLE 7.

STAGE OF THE ILLNESS ON ADMISSION: DISTRIBUTION OF CASES.

	Controls.		D cases.		D + A cases.	
	No.	Per cent. of total	No.	Per cent. of total	No.	Per cent. of total
All cases.						
Developed measles in hospital	2	0·9	—	—	—	—
Admitted before rash ...	8	3·4 } 19·7	7	2·9 } 17·8	13	5·9 } 23·9
,, 3rd day of rash and later	38	16·2 }	36	14·9 }	40	18·0 }
,, 1st day of rash ...	118	50·4	133	55·2	99	44·6
,, 2nd day of rash ...	68	29·1	65	27·0	70	31·5
Cases under 2 years old.						
Developed measles in hospital	2	0·9	—	—	—	—
Admitted before rash or 3rd day and later ...	15	6·4	18	7·5	29	13·2
,, 1st day of rash ...	48	20·5	56	23·2	35	15·8
,, 2nd day of rash ...	30	12·8	21	8·7	28	12·6

TABLE 8.

SEX: DISTRIBUTION OF CASES.

	Controls		D cases		D + A cases	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Males ...	124	53	119	49	122	55
Females ...	110	47	122	51	100	45

larger proportion of children under two years old who were seriously ill on admission, and that this factor contributed to the higher fatality rate among them.

One more factor requiring consideration is the sex distribution since the fatality rate was higher among boys than among girls. There were 365 males, of whom 20 or 5·5 per cent., died; and 332 females, of whom 13, or 3·9 per cent., died. As shown in table 8, the distribution of males and females was dissimilar in the three groups, and again the D plus A group was at a small disadvantage: the D group contained 49 per cent. males, the controls 53 per cent., and the D plus A group 55 per cent.

It so chanced, therefore, that the D plus A group was at a disadvantage in the sex and seasonal distribution of cases, and in the stage of the disease at which the children were admitted, and the D group on the other hand was more favourably placed than the other two groups as regards sex distribution and stage of admission. This may explain the higher fatality rate among the D plus A cases, but these differences were not sufficiently great in themselves to wipe out a favourable influence of treatment with vitamin A and D on the fatality rate, had any such occurred.

Incidence of pneumonia after admission.—Even though treatment with these vitamins did nothing to prevent death (and the majority of deaths were from pneumonia already present on admission) it might have had a favourable effect in diminishing complications occurring after admission. As regards pneumonia, its incidence after admission was similar among controls and D plus A cases, but it was considerably lower in the D group (see table 9). Thus vitamin A administration did not lessen this complica-

TABLE 9.

PNEUMONIA DEVELOPING AFTER ADMISSION.

	CONTROLS		D CASES		D + A CASES	
	NO. OF CHILDREN WITHOUT PNEUMONIA ON ADMISSION	NO. WHO DEVELOPED PNEUMONIA	NO. OF CHILDREN WITHOUT PNEUMONIA ON ADMISSION	NO. WHO DEVELOPED PNEUMONIA	NO. OF CHILDREN WITHOUT PNEUMONIA ON ADMISSION	NO. WHO DEVELOPED PNEUMONIA
TOTAL	203	13	212	4	194	12
PERCENTAGE		6·4		1·9		6·2

tion. It can only be argued that vitamin D did so if it is supposed that vitamin A in the dosage given had a harmful effect, so wiping out the benefit accruing from vitamin D in the D plus A group, and this on the face of it is most unlikely.

The difference, however, between the controls and D cases is only of 2·12 times its standard error so that the odds against it having arisen merely by chance are not very large.

Incidence of otorrhoea after admission.—One of the medical officers (H. L.) examined the ear drums of all children admitted to three out of the five wards, and found catarrhal or inflammatory changes to be almost as constant a feature in the ear as they were in the conjunctivae. No attempt

has been made to grade these changes, but the patients have been divided according to whether or not they developed otorrhoea.

On admission the case incidence of otorrhoea was similar in the three groups: controls 3·0 per cent.; D cases 3·7 per cent.; and D plus A cases 3·2 per cent. The total incidence (before and after admission) was greater in the vitamin-treated groups; the figures being, control group 12·4 per cent., D cases 15·8 per cent., and D plus A cases 17·1 per cent. Table 10 shows

TABLE 10.

INCIDENCE OF OTORRHOEA.

	CONTROLS				D CASES				D + A CASES			
	No. OF CHILDREN	No. OF CHILDREN WITH OTORRHOEA			No. OF CHILDREN	No. OF CHILDREN WITH OTORRHOEA			No. OF CHILDREN	No. OF CHILDREN WITH OTORRHOEA		
		On admission	After admission	Total		On admission	After admission	Total		On admission	After admission	Total
TOTAL CASES ...	234	7	22	29	241	9	29	38	222	7	31	38
PER CENT. ...	...	3·0	9·4	12·4	...	3·7	12·0	15·8	...	3·2	14·0	17·1
CHILDREN WITHOUT OTORRHOEA ON ADMISSION	227		22		232		29		215		31	
PER CENT. ...	...		9·7		...		12·5		...		14·4	

the percentage of children who were admitted without otorrhoea and developed it after admission; the figures are, controls 9·7 per cent., D cases 12·5 per cent., and D plus A cases 14·4 per cent. Again the D plus A group comes out worst. Presumably the factors which have already been noted as placing the D plus A group at a slight disadvantage played their part here also, but these differences in incidence of otorrhoea after admission are not more than might easily have arisen by chance.

Incidence of all complications excluding skin lesions.—An attempt was made to assess the incidence of all complications which developed after admission, and this is set out in table 11. Here the results are less certain, because the dividing line between, for example, changes in the mouth ordinarily occurring in measles and a stomatitis which should be reckoned as a complication is absolutely arbitrary. Even in view of this difficulty, it would be expected that if any marked discrepancy in the incidence of such complications existed between the three groups it would show itself.

Actually the differences are small. In table 11 the incidence of complications is shown as the incidence per 1,000 child-days for complications affecting respectively the eyes, mouth, throat and nose, ears, larynx and bronchi, and lungs, as well as for other complications. The largest difference is for pneumonia which has already been considered. The total incidence of complications occurring after admission per 1,000 child-days is, controls 32·1, D cases 30·1, and D plus A cases 34·8, rates which considering the number of children in each group are remarkably similar and show no advantage

TABLE 11.

INCIDENCE OF COMPLICATIONS WHICH DEVELOPED AFTER ADMISSION.

(Cross infections with other fevers excluded.)

	No. of children	Days of observation	Infections after admission. Eyes	Mouth	Throat and nose	Ears*	Larynx and bronchi	Lungs	Other infections	Total attacks combined
CONTROLS.										
No.	234	4451	11	24	30	30	11	13	24	143
ATTACKS PER 1,000 CHILD-DAYS	—	—	2·5	5·4	6·7	6·7	2·5	2·9	5·4	32·1
D CASES.										
No.	241	4348	9	16	20	40	9	4	33	131
ATTACKS PER 1,000 CHILD-DAYS	—	—	2·1	3·7	4·6	9·2	2·1	0·9	7·6	30·1
D + A CASES.										
No.	222	4193	12	24	23	45	11	12	19	146
ATTACKS PER 1,000 CHILD-DAYS	—	—	2·9	5·7	5·5	10·7	2·6	2·9	4·5	34·8
D CASES AND D + A CASES COMBINED.										
No.	463	8541	21	40	43	85	20	16	52	277
ATTACKS PER 1,000 CHILD-DAYS	—	—	2·5	4·7	5·0	10·0	2·3	1·9	6·1	32·4

* Double otorrhoea has been reckoned as two 'attacks.'

to the vitamin-treated groups. Children admitted on the day of appearance of the rash were separately considered. In practice this is the stage of the disease at which the majority of cases are diagnosed. Again it was found that the incidence of complications after admission was closely similar in the three groups.

Duration of pyrexia after appearance of rash.—If the incidence of secondary infections was higher in one group than in the others, one would expect this to be reflected in an increase in the length of the average pyrexial

period for that group. Table 12 shows the average number of days of pyrexia for each group, counting from the day of the rash. A child coming in with pyrexia on the fourth day from the appearance of the rash and continuing to have a temperature above normal for another three days, would be reckoned as having seven days of pyrexia, though only in hospital for three of those seven days. On the other hand, a child coming in with a normal temperature six days after the appearance of the rash was omitted from the tables because there was no information available as to the duration of the pyrexia. In all eleven patients were omitted. The average number of days of pyrexia after the appearance of the rash was as follows: controls 6·6 days, D cases 6·2 days, and D plus A cases 6·5 days. Hence these figures provide no evidence of any favourable effect on the course of this disease from the vitamins given.

TABLE 12.

DAYS OF PYREXIA AFTER APPEARANCE OF RASH.

	No. of cases	Days of pyrexia	Average days of pyrexia
Controls	229	1,509	6·6
D cases	237	1,461	6·2
D + A cases ...	221	1,443	6·5

Incidence of skin lesions.—The estimation of skin lesions is again a subjective matter—for there is the constantly recurring problem as to whether the conditions recorded should be reckoned as one lesion or several. A child may develop a boil, this may clear up and subsequently he develops an abscess elsewhere. This would be reckoned as two lesions. On the other hand, if the child had multiple boils at one time this would be reckoned as one lesion. Many other arbitrary distinctions had necessarily to be drawn. But as all analyses were made by one person (H. M. M. M.) it is hoped that the subjective factor did not operate for or against any one group. Table 13 shows the results. The total incidence of skin lesions per 1,000 child-days was, controls 21·34, D cases 22·77, and D plus A cases 20·99. When the larger subdivisions are compared, the incidence of skin lesions in the three groups is again similar. There is nothing to suggest that by giving vitamin A the susceptibility to skin lesions was diminished. An attempt was made to compare the duration of the different types of lesions in the three groups, but the data were inadequate.

Duration of time in hospital.—Children were usually kept in hospital until twelve days from the onset of the illness, or until they were free from all complications of the disease (including lesions of the skin) developed in hospital. Thus if giving the vitamin emulsion had any influence on the severity of complications, or the rate at which they cleared up, this should be reflected in a shortened stay in hospital. Four sets of figures are shown in table 14: (a) the average period in hospital for all cases (this included those who died, and those who were transferred to other wards for one

TABLE 13.

SKIN LESIONS DEVELOPED AFTER ADMISSION.

	Controls			D cases.			D + A cases		
	No. of attacks	No. per 1,000 child-days		No. of attacks	No. per 1,000 child-days		No. of attacks	No. per 1,000 child-days	
Lesions of napkin area :									
Erythema ...	2	0·45		6	1·38		2	0·48	
Papules	22	4.94		21	4·83		21	5·01	
Ulcers and scabs	9	2·02	8·31	13	2·99	9·20	9	2·15	8·59
Excoriation and pustules ...	6	1·35		6	1·38		6	1·43	
Nares : Excoriation, etc. ...	9	2·02		3	0·69		7	1·67	
Intertrigo or 'cracked ears'	5	1·12		7	1·61		5	1·19	
Dermatitis, pustules, ulceration, etc.	11	2·47	7.64	11	2·53	9·43	8	1·91	8·59
Boils, abscesses, septic fingers and toes	7	1.57		15	3·45		13	3.10	
Impetigo	2	0·45		5	1·15		3	0·72	
Infected abrasions and traumata...	1	0·22		—	—		1	0·24	
Papules (not napkin area) ...	19	4·27		11	2·53		11	2·62	
Herpes	2	0.45		1	0·23		2	0·48	

TABLE 14.

DURATION OF STAY IN HOSPITAL AND DURATION OF OBSERVATION.

	All cases.					Cases which recovered.				
	No. of cases.	Days in hospital.	Average.	Days of observation.	Average.	No. of cases.	Days in hospital.	Average.	Days of observation.	Average.
Controls ...	234	5743	24·5	4451	19·0	224	5658	25·3	4344	19·4
D Cases ...	241	5649	23·4	4348	18·0	231	5430	23·5	4195	18·2
D + A Cases	222	5188	23·4	4193	18·9	208*	5062	24·3	4071	19·6

*Table I shows for Group D + A a total of 222 children with 13 deaths, leaving 209 cases. Of these, however, one child developed diphtheria while under observation, was transferred to another ward, and died 16 days after transfer, from pneumonia. Hence the figures for recoveries is shown here as 208.

reason or another and from that time ceased to be included in this observation); (b) the average period of observation for all cases; (c) the average period in hospital of the children who recovered (this provides the best figures for comparison for the purpose of this analysis as the average is not shortened by the inclusion of children dying in the first week); and (d) the average period of observation of the children who recovered. Whichever set of figures is considered the averages are close.

The frequency distributions of days of observation are shown in table 15. There is a suggestion of a deficit of short cases in the controls,

TABLE 15.

FREQUENCY DISTRIBUTIONS OF DAYS OF OBSERVATION.

DAYS OF OBSERVATION	CONTROLS PER CENT.	D CASES PER CENT.	D + A CASES PER CENT.
7 - 14 DAYS ...	46	55	49
15 - 24 ,, ...	38	29	31
25 - 34 ,, ...	8	11	11
35 DAYS AND OVER	8	5	9

balanced by an excess in the 15–24 day group, but no consistent difference in prolonged cases. Statistically the differences are such as might easily arise by chance. The mean times of observation, as calculated from the frequency distribution, are: controls 19·02 days (standard deviation 10·89); D cases 17·74 days (standard deviation 9·90); and D plus A cases 19·08 days (standard deviation 11·35). The means for the control and for the D plus A groups are almost identical. The means for the control and D groups differ by 1·28 days, which has a standard error of 0·98, and is therefore not more than might be due to chance.

Discussion.

One conclusion emerges from the findings set forth, namely, that neither vitamin D, nor vitamins D plus A combined, as here given, had any favourable influence on the course of measles or on its complications during the period the children were under observation. Such results might indicate that few, if any, of the children suffered from a deficiency of either of these vitamins, that though such a deficiency existed it was without effect on the course of measles, or simply that treatment with the vitamins was begun too late and was of too short duration for any effect to be obvious.

Taking these possibilities in order it may be stated that none of the children suffered from obvious vitamin A deficiency; none, for example, had xerophthalmia, nor skin changes which could be diagnosed as phrynoderma or 'papular dry skin.' No tests were made for night blindness. Hence

there is no proof of vitamin A deficiency among the patients. All the children were examined clinically for evidence of rickets past or present. Three had active rickets as shown by the presence of craniotabes. Of the rest, there were thirty-three cases noted as having rickets or ' probable rickets,' or ' ? old rickets.' In the great majority of these the bony stigmata present were slight, so that the existence of rickets, past or present, was often in doubt, and if the clinical findings, the age of the children, and the season are taken into consideration the proportion with active rickets at the time of admission must have been small. It can, therefore, be concluded that none of the children suffered from overt vitamin A deficiency, and very few from overt vitamin D deficiency at the time of admission. Whether or not they suffered from minor grades of deficiency insufficient to produce obvious clinical changes is an open question.

The second possibility, that deficiencies of these vitamins are without influence on the course of measles, is, on the face of it, improbable. There is much to indicate that a deficiency of either vitamin D or vitamin A will increase susceptibility to some infections[2, 4] and, if so, a diminished resistance to the complications of measles would certainly be expected.

There are various arguments that can be brought forward in favour of the third possibility, namely, that treatment with vitamins was begun too late and was of too short duration to produce obvious results even had vitamin deficiency been present. If it is assumed that the rash usually appears on the fourth day, then 50 per cent. of the present patients started treatment on the fourth day of the disease, and a further 31 per cent. on or after the fifth day. Moreover, the average period of observation was under twenty days. If this is compared with the time needed to produce an effect in rickets, then the earliest radiographic evidence of healing in an overt case of rickets with optimum treatment generally appears in the third week, and may be delayed until the fourth week. Proof of improved general health may be delayed much longer. If vitamin A deficiency is considered, as revealed by ' papular dry skin,' in the only overt case heretofore under the personal observation of one of us, no improvement in the skin condition was apparent until approximately two weeks after treatment with vitamin A was begun[6].

Thus though the results of vitamin treatment were negative, this cannot be claimed as evidence that the children under observation had been receiving a sufficiency of vitamins A and D, nor as evidence that a deficiency of these vitamins, should it exist, is without influence on the course of measles. However, so far as the evidence goes, no benefit is to be expected from giving vitamin A or D to children admitted in the ordinary way to the

fever hospitals, i.e., usually after the appearance of the rash (which is generally reckoned as appearing on the fourth day of the disease) and for an average period of about three weeks.

Summary.

The effect of giving vitamin D, and vitamin D plus A, to children with measles was investigated on 697 cases under thirteen years of age at the North Eastern Hospital, London. The 697 cases were divided into three groups. The first group served as controls and had the ordinary ward diet only, the second group received in addition 3,000 international units of vitamin D daily as an emulsion of calciferol, and the third received the same amount of vitamin D, with, in addition, vitamin A equivalent to six drachms of cod-liver oil of a blue value of 7·5.

Comparison shows that on admission the children were fairly evenly divided between the three groups as regards age, incidence of pneumonia, and incidence of otorrhoea. They were also evenly distributed as regards the wards in which they were treated and the medical officers under whose charge they came. It so chanced that the D plus A group was at a slight disadvantage as regards sex and seasonal distribution and the stage of the disease at which the children were admitted, and the D group was slightly more favourably placed as regards sex distribution and the stage of admission. These differences were, however, slight. A comparison of fatality rates, of incidence of pneumonia, of otorrhoea, of all complications and of skin lesions developed in hospital, as well as a comparison of duration of pyrexia or of length of stay in hospital, affords no evidence of any favourable effect exerted on the course of the disease by giving either vitamin D or vitamins D plus A combined. It is pointed out that this negative result may be due (a) to the fact that the time of observation (average under twenty days) may have been too short to demonstrate any effect from vitamin therapy, and (b) that the treatment may have been started too late since in 81 per cent. of the cases treatment was not started until after the appearance of the rash, say till the fourth day or later in the disease.

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